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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/992,860	11/14/2001	Kuang Yu Chen	RU-0173	6007

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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	**PAPER NUMBER**
1655	

DATE MAILED: 09/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/992,860	CHEN ET AL.	
	Examiner	Art Unit	
	Michele Flood	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *38-74* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/30/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the Applicant's "REMARKS" and the Declaration under 37 C. F. R. § 1.132 filed by Dr. Chi-Tang Ho on June 30, 2006.

Claims 38-74 are under examination.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-74 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of inhibiting the growth of cancer cells comprising administering an effective dose amount of a composition comprising a mixture of theaflavin-3-gallate and theaflavin-3'-gallate to cancerous cell lines and/or an *in vivo* method of inhibiting the growth of cancer cells in mice comprising administering to mice an effective dose amount of a composition comprising a mixture of theaflavin-3-gallate and theaflavin-3'-gallate, does not reasonably provide enablement for a method of treating colorectal cancer or a method of treating colorectal cancer in a human, wherein the method suppresses the growth of cancerous colon cells in the human or a method of treating premalignant colorectal adenoma in a human or a method of treating premalignant colorectal adenoma, wherein the method suppresses

the growth of premalignant colorectal adenoma cells in a human or a method of preventing colorectal cancer in a human or a method of preventing colorectal cancer in a human, wherein the method suppresses the growth of colon cells in a human comprising administering to a human an effective amount of theaflavin-3-gallate and theaflavin-3'-gallate to a human in need thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Full consideration was given to each of Applicant's arguments and the Declaration under 37 C. F. R. § 1.132 filed by Dr. Ho. However, the rejection remains for the reasons set forth in the previous Office action and for the reasons set forth herein.

The claims are drawn to a method of treating colorectal cancer in a human comprising administering an effective amount of theaflavin-3-gallate and theaflavin-3'-gallate to a human in need thereof; a method of treating colorectal cancer in a human comprising administering to a human in need thereof theaflavin-3-gallate and theaflavin-3'-gallate to a human in an amount to suppress the growth of cancerous colon cells in the human; a method of treating premalignant colorectal adenoma in a human comprising administering an effective amount of theaflavin-3-gallate and theaflavin-3'-gallate to a human in need thereof; a method of treating premalignant colorectal adenoma in a human in need thereof theaflavin-3-gallate and theaflavin-3'-gallate to a human in need thereof in an amount sufficient to suppress the growth of premalignant colorectal adenoma cells in the human; a method of preventing colorectal cancer in a human comprising administering an effective amount of theaflavin-3-gallate and

theaflavin-3'-gallate to a human in need thereof; a method of preventing colorectal cancer in a human comprising administering to a human in need thereof theaflavin-3-gallate and theaflavin-3'-gallate in an amount sufficient to suppress the growth of colon cells in the human.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2D 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

Applicant's main argument is directed to the idea that the Examiner has not come forward with any particular evidence as to why black tea extract would necessarily act differently in the human body than to human colon cancer cells. Firstly, Applicant argues that data demonstrating the enablement of the claimed invention is present in the application as it was originally filed. Applicant also directs the Examiner to the 132 Declaration, particularly paragraphs 6.2-6.3 and Exhibit 2.

With regard to the Declaration under 37 C. F. R. § 1.132 filed by Dr. Ho, full consideration was given to each statement and the teachings of the references cited therein. While Ho emphasizes that the results in Lu (C15, Lu et al. Cancer Res. 2000 Nov 15, 15:60(22): 6465-71. Differential effects of theaflavin monogallates on cell

growth, apoptosis and Cox-2 gene expression in cancerous versus normal cells.) in large part mimic the results present in the instant specification, nowhere in the Declaration does Ho substantiate a correlation for a relationship disclosed in the present application or the data presented in Lu, which both used *in vitro* assays to demonstrate that the claim-designated composition exhibited differentia inhibiting effects on human cancer cells, to constitute a working example to enable the skilled artisan to make and/or use the claimed method of treating and/or preventing the claim-designated colorectal cancers in a human. For instance, at 6.4 of the Declaration, Ho merely states, "In view of the foregoing, I conclude, and it is my opinion that others skilled in the art would also conclude that, based on the differential effects of TF-2 on normal and cancer cells and the specific effect of cox-2 gene expression, TF-2 is useful for the treatment and prevention of colorectal cancer." The Office notes that Ho does not express that one of skill in the art would conclude from the disclosure of Applicant's specification as originally filed that the instantly claimed invention provides enablement for the treatment and/or prevention of the claim-designated cancer diseases. Furthermore, the Office notes that on page 6470, Column 2, last line of the Lu' reference, Lu merely states, "These features make TF-2 a useful compound for further evaluation as a potential therapeutic reagent."

Applicant argues, "Applicant points out that the Examiner's arguments on a lack of predictability essentially amount to an allegation of lack of utility." Applicant further argues that the statements of Dr. Ho in the Rule 1.132 Declaration and Exhibit 3 provide further evidence of utility and enablement of the instantly claimed invention. Each of

Applicant's arguments, as well as the statements of made by Dr. Ho in the 1.132 Declaration, have been thoroughly considered but they are neither persuasive nor commensurate in scope to the limitations of the instantly claimed invention with particular regard to Applicant's disclosures set forth in the present specification as originally filed or the issues of the rejection for all of the reasons set forth in the previous Office action and for all of the reasons set forth herein. For example, on page 8 of Applicant's "REMARKS" filed on June 30, 2006, Applicant asserts that the Examiner has failed to establish a *prima facie* case of lack of enablement in the previous Office action. Nevertheless, Applicant is invited to revisit page 2 of the previous Office action bridging page 6, wherein the present claims were rejected under 35 U.S.C. 112, first paragraph. Moreover, as the teachings of Huang (Exhibit 3, C13, Huang et al. Effect of black tea theaflavins on 12-O-tetradecanolyphorbol-13- acetate-induced inflammation. Ch. 24 of *Herbs: Challenges in Chemistry and* Biology. Wang et al. eds. American Chemical Society, 2006, Washington, DC, pp. 314-325.) post-date the date of the filing of the instant specification as originally filed, Applicant cannot rely on the teachings of Huang to provide enablement of the instantly claimed invention. Given the foregoing and given that the Examiner properly interpreted the claims and their accompanying disclosure under the *in re Wands* factor analysis to determine whether undue experimentation is required to enable any person skilled in the art to make and/or use the invention commensurate in scope to the limitations in the claims, Applicant's arguments are found unpersuasive; and, therefore, the Office deems that the Examiner has met the initial burden because clear reasons for lack of enablement were given and

clear reasons were given for a conclusion of lack of a correlation of the data obtained by an *in vitro* cancer cell assay as disclosed in the examples presented in Applicant's disclosure would necessarily substantiate or to translate into *in vivo* method of treating and/or preventing the claim-designated colorectal cancers in a human.

Nonetheless, Applicant may continue to argue otherwise. For instant, Applicant makes reference to the case law of *in re* Brana. However, at present, the facts of *in re* Brana do not apply to the instant issues because the Court's finding was based not on as issue of enablement of a claimed invention but the usefulness of an invention in the meaning of patent law. Herein, as well as in the previous Office action, the Examiner has not imposed a 35 U. S. C. 101 rejection of the instantly claimed invention. Instead, the claims were rejected under 35 U.S.C. 112, first paragraph, which addresses matters other than related to the question of whether or not an invention lacks utility. Thus, Applicant's arguments are not commensurate in scope to the instant issue and the facts of the case law of *in re* Brana are misapplied.

While Applicant argues that the Examiner has not come forward with any particular evidence as to why black tea extract would necessarily act differently in the human body than to human colon cancer cells, it is clear from Applicant's limited disclosure of the present specification that Applicant was not in full possession of the instantly claimed invention, as broadly claimed, at the time of filing of the instant specification. The Office reiterates that Claims 38-74 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of inhibiting the growth of cancer cells comprising administering an

effective dose amount of a composition comprising a mixture of theaflavin-3-gallate and theaflavin-3'-gallate to cancerous cell lines and/or an *in vivo* method of inhibiting the growth of cancer cells in mice comprising administering to mice an effective dose amount of a composition comprising a mixture of theaflavin-3-gallate and theaflavin-3'-gallate, does not reasonably provide enablement for a method of treating colorectal cancer or a method of treating colorectal cancer in a human, wherein the method suppresses the growth of cancerous colon cells in the human or a method of treating premalignant colorectal adenoma in a human or a method of treating premalignant colorectal adenoma, wherein the method suppresses the growth of premalignant colorectal adenoma cells in a human or a method of preventing colorectal cancer in a human or a method of preventing colorectal cancer in a human, wherein the method suppresses the growth of colon cells in a human comprising administering to a human an effective amount of theaflavin-3-gallate and theaflavin-3'-gallate to a human in need thereof, much less a method of prevention of the claim-designated cancers. Moreover, the instant application does not provide a working example providing data, which shows that the composition of the instant claims would indeed prevent an event such as the claimed designated disease disorders. While Applicant may argue that the teachings of Exhibit 3 (C13, Huang et al.) and the statements made in the Rule 132 Declaration of Dr. Ho provide evidence of enablement of the instantly claimed invention, and that the *in vivo* data presented in the Rule 1.132 Declaration shows that the data obtained from cancer cell lines was indicative of what would happen in an animal, the Office respectfully disagrees. Such reliance on a reference post-dating the filing of the

instantly claimed invention is impermissible and fails to remedy the lack of enabling features in the present specification as originally filed to provide direction and guidance on how to practice the invention and working examples absent therein to demonstrate the effect of theaflavin 3-gallate and theaflavin-3' gallate on colon carcinogenesis *in vivo*.

The Examiner agrees with Applicant that one of skill in the art at the time the application was filed would have recognized cancer cell lines as *in vitro* models of human cancer. Nonetheless, the Office maintains that the state of the art at the time of filing of the present application suggested that the delivery of therapeutic drugs which exhibit *in vitro* anti-tumor activity do not necessarily have the same beneficial functional effect in humans. For example, Jain (Science, 1996. Vol. 271: 1079-1080) discloses that while promising chemotherapeutic agents exhibit activity against cancer cells *in vitro* and *in vivo* tumor systems, these same agents heralded as breakthrough drugs do not have the same functional effect in humans when delivered to humans bearing tumors. Because of the known unpredictability of the art, in the absence of appropriate experimental evidence, no one skilled in the art would accept the assertion that the claimed administration of the claim-designated ingredients could function as contemplated in the specification, as broadly claimed by Applicant. In another example, Dermer (Bio/Technology, 1994. Vol. 12: 320) states, "The cell lines in which cancer is usually studied are unsuitable for the job. They do not mimic conditions in the human body."

There is no guidance in the specification, other than the aforementioned examples directed to the delivery of an effective amount of black tea extract which comprises a mixture of theaflavin-3-gallate and theaflavin-3'-gallate to *in vitro* cancer cell cultures for the reduction of cell number and decrease in the level of Cox-2 protein. Hence, given the insufficient guidance in the specification as to how to carry out the instantly claimed invention for the proposed method of therapeutic and/or prophylactic treatment of the claim-designated colorectal disease conditions in a human in need thereof comprising the administration of an effective amount of theaflavin-3-gallate and theaflavin-3'-gallate to a human in need thereof, the lack of working examples, and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan to practice the instantly claimed invention, as broadly claimed by Applicant.

Moreover, there is insufficient disclosure to reasonably predict that the instantly claimed methods of treating and/or preventing the claim-designated colorectal cancers in a human comprising the administration of the claim-designated composition would indeed suppress the growth or prevent the growth or inhibit the growth of various colorectal cancers and adenomas in a human. This is merely an unsubstantiated assertion with no evidence to support the contention that the *in vitro* studies of the specification are indicative of *in vivo* activity. Applicant has only shown cell culture data, not treating cancer bearing patients or patients at risk of developing the claim-designated cancers or shown an art recognized correlation between the data shown and the scope of the claimed invention. The artisan would recognize and appreciate

that there is no known correlation between *in vitro* results and *in vivo* results, because the artisan recognizes that an *in vitro* assay cannot duplicate the complex conditions of *in vivo* therapy or *in vivo* prophylaxis. In the *in vitro* assay, the agent is contact with cells during the entire exposure period. This is not the case *in vivo* where exposure to the target site may be delayed or inadequate. In addition, variables such as biological stability, half-life, or clearance from the blood are important parameters in achieving successful therapy. During administration, the composition may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation or immunological inactivation. In addition, during administration, the composition may not reach the target cells where its activity is to be exerted, may be absorbed by fluids, cells, and tissues where the composition has no effect and/or a large enough local concentration may not be established. There are no specific teachings in the disclosure that would allow one of skill in the art to have a reasonable expectation of success in transferring the *in vitro* method to treat and/or prevent the claim-designated colorectal cancer disease conditions and/or cancer cells in a human. While Applicant may argue that the Min mouse used in the studies of Huang (Exhibit 3, C13, Huang et al.) correlates to an appropriate *in vivo* model for testing inhibitory for testing compounds inhibitory to cox-2 gene expression in human colorectal cancer tissues, the Office notes that Huang teaches the oral administration of black tea extract enriched with a mixture of theaflavins, which included the claim-designated theaflavins as well as theaflavins other than the claim-designated theaflavins, to provide a method of inhibiting the formation of colorectal tumors, small intestinal tumors and large intestinal tumors. Even

in view of the data obtained in the aforementioned reference, even Huang insists, "More studies are needed to determine the bioavailability and anti-carcinogenic effects of black tea and theaflavin rich black tea." *See* page 325, Column 1, last line. One is only left with speculation and an invitation to experiment. Given the foregoing, it appears that Applicant's instantly claimed invention is no more than a germ of an idea.

According, it would take undue experimentation without a reasonable expectation of success to determine which amounts of the claim-designated composition would have the claimed functional effect for treating and or preventing colorectal cancer or premalignant colorectal adenoma in a human in need thereof comprising administering to the human a composition comprising a mixture of theaflavin-3-gallate and theaflavin-3'-gallate in an amount sufficient to suppress the growth of cancerous colon cells in a human or suppress the growth of premalignant colorectal adenoma cells in a human, and wherein the composition further comprises an orange peel, as broadly claimed, other than the demonstrated *in vitro* and/or *in vivo* method of treating cancer in mice.

Any inquiry concerning this communication or earlier communications from the ----examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michele Flood
Primary Examiner
Art Unit 1655

MCF
September 18, 2006

MICHELE FLOOD
PRIMARY EXAMINER